Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Gopal AK, Kahl BS, de Vos S, et al. PI3Kδ inhibition by idelalisib in patients with relapsed indolent lymphoma. N Engl J Med;370:1008-18. DOI: 10.1056/NEJMoa1314583

Supplement to :

PI3Kδ Inhibition by Idelalisib in Patients with Relapsed Indolent Lymphoma

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SUPPLEMENTAL DATA

Patient Disposition

Of the 125 patients enrolled, 40 patients (32.0%) remain on therapy, 49 patients (39.2%) have completed treatment (41 patients [32.8%] due to PD and 8 patients [6.4%] due to death), and 36 patients (28.8%) have discontinued treatment as of the data cut-off date (25 June 2013). Among those who discontinued treatment, 25 patients (20.0%) discontinued due to adverse events, 4 patients (3.2%) withdrew consent, and 7 patients (5.6%) discontinued at the request of the investigator. Three of the 7 patients who discontinued at the request of the investigator were referred to undergo high-dose chemotherapy with stem cell transplantation.

Supplemental Table S1. Overall response rate (ITT analysis set), as determined by the Independent Review Committee and the study investigators

	Total (N = 125)	
Best Overall Response	IRC Assessment	Investigator Assessment
CR	7 (5.6)	7 (5.6)
PR	63 (50.4)	64 (51.2)
MR	1 (0.8)	1 (0.8)
SD	42 (33.6)	41 (32.8)
PD	10 (8.0)	11 (8.8)
NE[a]	2 (1.6)	1 (0.8)
ORR[b]	71 (56.8)	72 (57.6)
95% CI[c]	47.6 – 65.6	48.4 – 66.4
P-value[d]	< 0.001	< 0.001
Agreement (%)[e]	84.8	

a Subject 138-09012 had no baseline or post-baseline tumor assessment determined by the IRC or the investigator. Subject 703-09085 had no post-baseline tumor assessment determined by the IRC.

b Patients who had a CR or PR (or MR for patients with WM) in best overall response category.

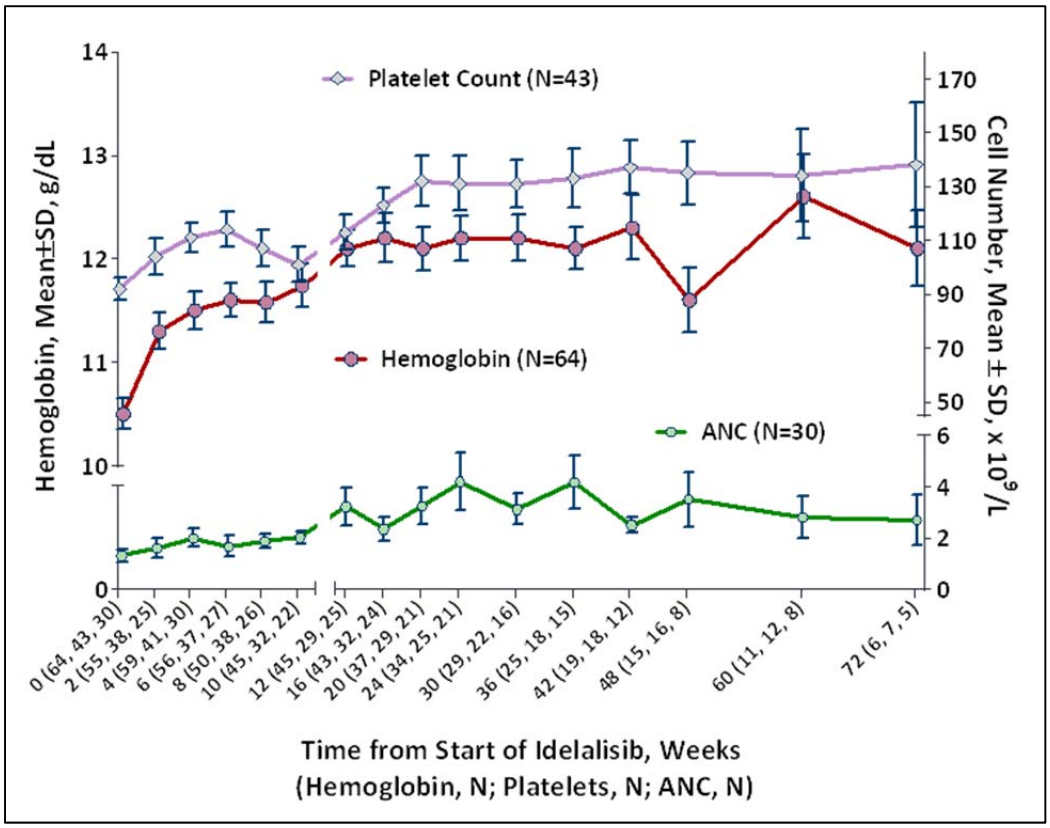
c 95% exact binomial confidence interval for ORR.

d 1-sided p-value for testing against the null hypothesis of ORR ≤ 20% (exact binomial test)

e Agreement between IRC/investigator for overall response (yes vs no)

Supplemental Figure S1

Blood hemoglobin (closed circles), platelet counts (diamonds), and absolute neutrophil count (open circles) during idelalisib treatment. Patients are those with baseline anemia (n = 64), thrombocytopenia (n = 43), or neutropenia (n=64) of Grade ≥1.



Supplemental Figure S2: Pharmacokinetics and Clinical Outcomes

Figure S2 shows the box plot of the relationship between idelalisib trough concentrations C_{trough} and overall response status, and also stratified by categories of response for all evaluable patients with pharmacokinetic data. Shown are medians (and labeled median values) with interquartile range box plots, with bars extending to 10-90% range. These analyses indicated that idelalisib C_{trough} was similar between patients with responding tumors (CR or PR) and those with nonresponding tumors (SD, PD and NE), as well as across the 4 evaluable response categories (excluding 2 patients with NE response status). These results indicated a lack of relationship between idelalisib exposure at 150 mg BID and best overall response. Additional logistic regression analysis further indicated a lack of relationship between idelalisib plasma exposures and response status (response vs non-response).

Methods: Plasma samples were collected for concentrations of idelalisib prior to dosing and 1.5 hours postdose at Weeks 1, 4, 8, and 16 for all subjects. In a subset of subjects, additional plasma samples were collected at predose, 0.5, 1.0, 1.5, 2.0, 3.0, 4.0, 6.0, 8.0, 10.0, and 12.0 hours postdose at Weeks 1 and 4. All available idelalisib concentration records were included in the pharmacokinetic analyses to build an idelalisib population pharmacokinetic model. Steady-state trough idelalisib concentrations were predicted based on the final population pharmacokinetic model for each subject following 150 mg BID and these trough concentrations were used to evaluate the relationship between exposure and response.

Figure S2. Exposure-Efficacy Relationship: Box Plot of Idelalisib C_{trough} Stratified by Best Overall Response on Study